

# Horizon Scanning in Oncology

Carfilzomib (Kyprolis<sup>®</sup>) for  
patients with relapsed multiple  
myeloma who have received  
one to three prior lines of  
therapy



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#### **DISCLAIMER**

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice nor should it be used for commercial purposes.

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# 1 Drug description

## Generic/Brand name/ATC code:

Carfilzomib/Kyprolis®/L01XX45

## Developer/Company:

Onyx Pharmaceuticals

## Description:

Carfilzomib (Kyprolis®) is an epoxomicin derivate that selectively and irreversibly binds and predominantly inhibits the chymotrypsin-like activity of  $\beta 5$  and LMP7 subunits of the 20S component of proteasome, an enzyme responsible for degrading a large variety of cellular proteins. Due to proteasome-mediated proteolysis inhibition, polyubiquinated proteins accumulate, which consecutively leads to cell-cycle arrest, induction of apoptosis and inhibition of tumour growth [1, 2].

Carfilzomib is administered intravenously (IV) over 2 to 10 minutes on two consecutive days each week for three weeks (on days 1, 2, 8, 9, 15 and 16), followed by a 12-day rest period (days 17 to 28); each 28-day period is considered one treatment cycle. During the first cycle, carfilzomib is administered at a dose of 20 mg/m<sup>2</sup>; if tolerated, the dose should be escalated to 27 mg/m<sup>2</sup> in cycle two and should be maintained in subsequent cycles. The treatment can be continued until disease progression or unacceptable toxicity [3]. If signs of dose intolerance occur, either the dose can be reduced to 20 mg/m<sup>2</sup> or the infusion time can be extended up to 30 minutes [4].

To reduce the risk of renal toxicity and of tumour lysis syndrome, patients who receive carfilzomib should be hydrated. Therefore, prior to each dose in cycle one, 250–500 ml of normal saline IV or another appropriate IV fluid should be given. If needed, an additional 250–500 ml of IV fluids can be administered following carfilzomib administration and the hydration can be continued in subsequent cycles. Adequate fluid volume status should be maintained throughout the treatment; blood chemistries and fluid overload need to be monitored [3].

Premedication with dexamethasone is required to reduce the incidence and severity of infusion reactions, which are characterised by fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness or angina. Prior to all administered doses of carfilzomib during cycle one and during the first cycle of dose escalation, dexamethasone should be given at a dosage of 4 mg (orally or IV). If infusion reactions develop or reappear during subsequent cycles, dexamethasone premedication (4 mg, orally or IV) should be administered again [3].

**carfilzomib is  
a tetrapeptide  
epoxyketone  
proteasome inhibitor**

## IV administration

**hydration prior to and  
following carfilzomib  
administration**

**premedication with  
dexamethasone**

## 2 Indication

**indicated in pretreated  
patients with multiple  
myeloma**

Carfilzomib (Kyprolis<sup>®</sup>) is indicated in patients with multiple myeloma who have received one to three prior therapies [3].

## 3 Current regulatory status

**EMA:  
not approved,  
orphan designation**

In 2008, the European Commission granted orphan designation for carfilzomib for the treatment of multiple myeloma [5]. On 18 December 2014, the EMA accepted the accelerated assessment request for carfilzomib (indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who received at least two prior therapies that included bortezomib and an immunomodulatory agent, or for whom such treatments are not appropriate) [6].

**FDA:  
approved since  
July 2012**

In July 2012, the FDA initially approved carfilzomib (Kyprolis<sup>®</sup>) under the provisions of accelerated approval regulations [7]. Carfilzomib was authorised for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy [8].

On 24 July 2015, the label was revised. Carfilzomib is now indicated [3]

- ✱ in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy.
- ✱ as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Moreover, the FDA granted carfilzomib priority review with the Prescription Drug User Fee Act (target action date 26 July 2015) [9].

## 4 Burden of disease

Multiple myeloma is a haematological malignancy characterised by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin.

Common symptoms at presentation include anaemia, bone pain, elevated creatinine/serum protein, fatigue/generalised weakness, hypercalcaemia and weight loss; the majority of symptoms are related to the infiltration of plasma cells (into the bone or other organs) or to kidney damage caused by excess light chains [10] (antibody subunits produced by neoplastic plasma cells).

The incidence of multiple myeloma in Europe is 4.5–6.0/100,000 per year; mortality is 4.1/100,000 per year [11]. Multiple myeloma is most frequently diagnosed among people aged 65 to 74 years; the median age at diagnosis is 69 years [2].

According to the European Society for Medical Oncology (ESMO) the diagnosis of multiple myeloma should be based on the following tests [5]:

- ✧ Detection and evaluation of the monoclonal component by serum and/or urine protein electrophoresis; nephelometric quantification of immunoglobulin (Ig)G, IgA and IgM; characterisation of the heavy and light chains by immunofixation; serum-free light-chain measurement
- ✧ Evaluation of bone marrow plasma cell infiltration: bone marrow aspiration and/or biopsies are the standard options to evaluate the number and characteristics. The bone marrow should be used for cytogenetic/fluorescence in situ-hybridisation studies and also has the potential for immunophenotypic and molecular investigations
- ✧ Evaluation of lytic bone lesions: a radiological skeletal bone survey (including spine, pelvis, skull, humeri and femurs) is necessary. A magnetic resonance imaging or computed tomography scan may be needed to evaluate symptomatic bony sites (even if the skeletal survey is negative and the patient has symptoms suggesting bone lesions). Moreover, magnetic resonance imaging provides greater detail and is recommended whenever spinal cord compression is suspected. Fluorodeoxyglucose positron emission tomography is currently under evaluation but should not be used systematically
- ✧ Complete blood cell count, including differential serum creatinine and calcium level.

For the diagnosis of multiple myeloma the following criteria must be met [5]:

- ✧ Clonal bone marrow plasma cells  $\geq 10\%$  or biopsy-proven plasmacytoma, and
- ✧ evidence of end-organ damage that can be attributed to the underlying plasma-cell proliferative disorder (CRAB criteria): hypercalcaemia (serum calcium  $> 11.5$  mg/dl), renal insufficiency (serum creatinine  $> 1.73$   $\mu\text{mol/dl}$  or estimated creatinine clearance  $< 40$  ml/min) anaemia (normochromic, normocytic with a haemoglobin value of  $\geq 2$  g/dl below the lower limit of normal or a haemoglobin value  $< 10$  g/dl) or bone lesions (lytic lesions, severe osteopenia or pathologic fractures).

Relapsed myeloma should be defined as clinically active disease in patients who have received one or more prior therapies and with disease not refractory to the most recent treatment. Refractory multiple myeloma refers to patients who never achieve minor response or better, including “non-responding

**neoplastic proliferation of plasma cells**

**median age at diagnosis: 69 years**

**tests for the diagnosis of multiple myeloma**

**diagnostic criteria**

**definitions of relapsed/refractory multiple myeloma**

but nonprogressing” patients (no significant change in M protein and no evidence of clinical progression) and “primary refractory, progressive disease” [12]. Relapsed-and-refractory disease is defined as relapse of disease in patients who must have achieved minor response or better, patients either become non-responsive while on salvage therapy or they progress within 60 days of last therapy. According to the International Myeloma Working Group, progressive disease is defined as an increase of > 25% from lowest response value in any one or more of the following [13]:

- ✧ Serum M-component and/or (the absolute increase must be  $\geq 0.5$  g/dL)
- ✧ Urine M-component and/or (the absolute increase must be  $\geq 200$  mg/24 h)
- ✧ Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved serum free light chain (FLC) levels. The absolute increase must be > 10 mg/dL
- ✧ Bone marrow plasma cell percentage; the absolute percentage must be  $\geq 10\%$
- ✧ Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- ✧ Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

#### staging/prognostic systems

There are two systems for the staging of multiple myeloma:

- ✧ The Durie-Salmon system, which has traditionally been used, differentiates 3 stages and, depending on kidney function/kidney damage, each stage is subclassified into A or B. This system is appropriate for assessing the extent of the disease or the size of the tumour [14]
- ✧ The International Staging System (ISS), which is based on the measurement of serum albumin and the levels of serum  $\beta_2$  microglobulin [15]:
  - ✧ Stage I: serum  $\beta_2$ -microglobulin < 3.5 mg/L, serum albumin  $\geq 3.5$  g/dL
  - ✧ Stage II: not stage I or III (serum  $\beta_2$ -microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL, or serum  $\beta_2$ -microglobulin 3.5 to < 5.5 mg/L irrespective of the serum albumin level)
  - ✧ Stage III: serum  $\beta_2$ -microglobulin  $\geq 5.5$  mg/L.

The Durie-Salmon system (developed in 1975) was widely adopted as the standard for multiple myeloma prognoses. In the 1980s, serum- $\beta_2$ -microglobulin was considered as the most powerful prognostic factor and reliable predictor of survival duration. Over time, various other prognostic factors, including conventional cytogenetics emerged, whereby deletion of chromosome 13 is the most significant prognostic abnormality. Due to their statistical power and their wide availability, serum  $\beta_2$ -microglobulin and serum albumin were selected from the various potential prognostic factors for the development of the ISS [15].

#### risk stratification

When patients are first diagnosed with multiple myeloma, stratification to high, intermediate or standard-risk disease is implemented, based on the results of fluorescence in situ hybridisation (FISH) for specific translocations and/or deletions, and conventional cytogenetics [16]. Generally, patients with a hypodiploid modal chromosome number including t(4;14)(p16;q32) or t(14;16)(q32;q23) are considered a high-risk group, hyperdiploid patients with (11;14)(q13;q32)



are considered a better prognostic group. When multiple myeloma progresses, it becomes more proliferative and a number of secondary chromosome aberrations develop [17]. According to the ISS, patients assigned to ISS stage 3 (serum  $\beta 2M \geq 5.5$  mg/l) have the poorest outcome [5].

In case of progressive disease, information on the initial response to therapy can be used to identify high-risk patients: patients who relapse less than 12 months from first-line therapy or relapse on therapy are considered to be high-risk patients even if their previous risk evaluation yielded standard risk. Conversely, in patients who were previously considered to have high-risk disease and who relapse more than two years from initial therapy, the disease can be considered as standard-risk disease at the time of relapse in the absence of new additional high-risk cytogenetic abnormalities [3]. Retrospective studies, including a retrospective analysis of 102 patients with relapsed multiple myeloma [18], demonstrated inferior survival in patients who relapse less than 12 months after initial therapy [3]. For patients who have high-risk disease at the time of relapse, participation in a clinical trial offers the best treatment. These patients may require more intensive treatment including prolonged maintenance therapy, multi-agent therapy, autologous stem-cell transplantation (ASCT) or consideration for allogeneic transplantation; particularly since these patients are not likely to respond to conventional therapies [3].

In terms of differential diagnosis, benign causes presenting with similar manifestations and other plasma cell dyscrasias need to be distinguished from multiple myeloma. The most common diseases to consider are monoclonal gammopathy of undetermined significance, smouldering multiple myeloma, Waldenström macroglobulinaemia, solitary plasmacytoma, primary amyloidosis, POEMS (osteosclerotic myeloma: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome and metastatic carcinoma [19].

#### **differential diagnosis**

## **5 Current treatment**

In patients with active myeloma, showing the CRAB criteria (hypercalcaemia  $> 11.0$  mg/dl, creatinine  $> 2.0$  mg/ml, anaemia: haemoglobin  $< 10$  g/dl, active bone lesions), and in patients who are symptomatic due to the underlying disease, front-line treatment should be initiated.

#### **front-line treatment**

According to the ESMO Guidelines, for patients who are not eligible for autologous stem cell transplantation (ASCT), an oral combination treatment with melphalan and prednisone plus novel agents (e.g. MPT: melphalan/prednisone/thalidomide or VMP: bortezomib/melphalan/prednisone) is considered as standard of care. Another option is bendamustine plus prednisone for patients who have clinical neuropathy at time of diagnosis [11].

Transplant-eligible patients receive induction therapy (bortezomib combined with dexamethasone) followed by high-dose therapy with ASCT. However, data from phase II studies showed, that the addition of a third agent to bortezomib/dexamethasone, such as thalidomide, doxorubicin, lenalidomide or cyclophosphamide (VCD) resulted in higher response rates [5].

**achieving disease control, amelioration of symptoms and improvement of quality of life are therapy goals**

The treatment aims of most patients with relapsed multiple myeloma are similar to those at the time of initial diagnosis: achievement of disease control, amelioration of symptoms and improvement of quality of life [20]. However, despite the increased number of available treatment options, side effects often limit the choices of a significant number of patients. For patients with early relapse, the introduction of thalidomide, bortezomib and lenalidomide changed the poor prognosis and the poor response to conventional chemotherapy they were deemed to have [7].

**ESMO:  
treatment of relapsed  
and refractory disease**

For the treatment of relapsed and refractory disease, the ESMO states the following [5]:

- ✱ in the relapse setting, the choice of therapy depends on several parameters such as age, performance status, comorbidities, previous treatment (type, efficacy, tolerance), number of prior treatment lines, available remaining treatment options and the interval since the last therapy
- ✱ lenalidomide has been approved by the EMA, in combination with dexamethasone and bortezomib either as single-agent or combined with pegylated doxorubicin
- ✱ in the relapse setting, bortezomib is mostly used in combination with dexamethasone
- ✱ thalidomide and bendamustine are frequently used and effective drugs, but not approved
- ✱ data from phase II trials showed effectiveness of triplet combinations; however, only one randomised trial showed the superiority regarding PFS of bortezomib, thalidomide and dexamethasone over thalidomide plus dexamethasone in patients relapsing after ASCT
- ✱ a second ASCT may be considered in young patients, providing that the patient responded well to the previous ASCT and had a PFS of more than 24 months
- ✱ in patients with relapsed multiple myeloma, allogeneic SCT should only be carried out in the context of a clinical trial
- ✱ if possible, patients should be offered to participate in clinical trials
- ✱ pomalidomide and carfilzomib are both approved in the U.S. but not yet available in Europe outside clinical trials
- ✱ other drugs or other classes of drugs (e.g. histone-deacetylase inhibitors or monoclonal antibodies are currently under development.

## 6 Evidence

A literature search was conducted on 18 May 2015 in four databases (Medline, Embase, CRD Database and The Cochrane Library). Search terms were “Carfilzomib”, “Kyprolis”, “Multiple myeloma”, “Relapsed multiple myeloma” and “Refractory multiple myeloma”. The manufacturer was contacted but did not submit any further evidence.

**396 references were identified by systematic literature search in 4 databases**

In total, 396 references were identified. Included in this report are:

- ✱ 1 phase III study, evaluating the efficacy and safety of carfilzomib with lenalidomide and dexamethasone compared with lenalidomide and dexamethasone in patients with relapsed multiple myeloma
- ✱ 6 phase II studies, described in chapter 6.2.

Phase I studies, compassionate-use studies, case reports and case series of carfilzomib were not included in this assessment.

### 6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title			
Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma [12, 21]			
Study identifier	NCT01080391, EudraCT number: 2009-016839-35, Onyx-ID: ASPIRE trial (PX-171-009)		
Design	Randomised, open-label, multicentre, phase III study		
	Duration	<i>Enrolment:</i> 2010-07 to 2012-03 <i>Median follow-up:</i> 32.3 months (carfilzomib with lenalidomide and dexamethasone), 31.5 months (lenalidomide and dexamethasone alone) <i>Cut-off date for interim analyses:</i> 2014-06-16	
Hypotheses	Superiority		
Funding	Onyx Pharmaceuticals		
Treatment groups	Intervention (n=392)	Carfilzomib as a 10-minute infusion on days 1, 2, 8, 9, 15 and 16 (starting dose 20 mg/m <sup>2</sup> on days 1 and 2 of cycle 1, target dose 27 mg/m <sup>2</sup> thereafter) during cycles 1 through 12 and on days 1, 2, 15 and 16 during cycles 13 through 18, after which carfilzomib was discontinued Lenalidomide (25 mg) was given on days 1 through 21 Dexamethasone (40 mg) was administered on days 1, 8, 15 and 22 Pre-treatment and post-treatment IV hydration (250 to 500 ml) was required during cycle 1 (and optional in subsequent cycles)	
	Control (n=389)	Lenalidomide (25 mg) was given on days 1 through 21 Dexamethasone (40 mg) was administered on days 1, 8, 15 and 22 Pre-treatment and post-treatment IV hydration (250 to 500 ml) was required during cycle 1 (and optional in subsequent cycles)	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Defined as the duration in months from randomisation to documented progressive disease or death due to any cause, whichever occurred earlier
	Overall survival	OS	Defined as the duration in months from the date of randomisation to the date of death due to any cause

	Overall response rate	OR R	Defined as the proportion of patients in each group who achieved stringent complete response (sCR), complete response (CR), very good partial response, or partial response as their best response assessed by International Myeloma Working Group (IMWG) criteria
<b>Endpoints and definitions</b> (continuation)	Duration of response	DO R	For patients achieving partial response or better, defined as the duration in months from the start date of response to the earlier date of documented progressive disease or death due to any cause
	Health-related quality of life	-	Assessed with the use of the European Organisation for Research and Treatment of Cancer Quality of Life Core Module (QLQ-C30) questionnaire on day 1 of cycles 1, 3, 6, 12, 18 and approximately 30 days after the last treatment
	Safety	-	Data on adverse events were collected until 30 days after administration of the last dose of study treatment, and events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
	Clinical benefit rate	-	Defined as the proportion of patients who achieved a best response of partial response or better according to International Myeloma Working Group Uniform Response Criteria or minimal response according to European Group for Blood and Marrow Transplant criteria
	Time to progression	-	Defined as the duration in months from the date of randomisation to the date of documented disease progression
	Time to next treatment	-	Defined as the duration in months from the date of randomisation to the date of initiating subsequent anti-myeloma therapy
<b>Results and analysis</b>			
<b>Analysis description</b>	526 events (disease progression or death) were required to provide 90% power to detect a 25% reduction in the risk of disease progression or death (HR of 0.75) at a one-sided significance level of 0.025. An interim analysis was to be performed after approximately 420 events had occurred (80% of the planned total). An O'Brien-Fleming stopping boundary for efficacy was calculated with the use of a Lan-DeMets alpha spending function on the basis of the number of events observed at the data-cutoff date. All reported P values are two-sided. Safety analysis included all patients who received at least one dose of the study treatment.		
<b>Analysis population</b>	Inclusion	<ul style="list-style-type: none"> <li>✳ Adults with relapsed multiple myeloma and measurable disease who had received 1–3 prior treatments</li> <li>✳ Patients previously treated with bortezomib were eligible provided that they did not have disease progression during treatment</li> <li>✳ Patients previously treated with lenalidomide and dexamethasone were eligible so long as they did not discontinue therapy because of adverse effects, have disease progression during the first 3 months of treatment, or have disease progression at any time during treatment if lenalidomide plus dexamethasone was their most recent treatment</li> <li>✳ All patients had adequate hepatic, haematologic and renal function (creatinine clearance <math>\geq 50</math> ml/minute) at screening</li> </ul>	
	Exclusion	<ul style="list-style-type: none"> <li>✳ Grade 3 or 4 peripheral neuropathy (or grade 2 with pain) within 14 days before randomisation</li> <li>✳ New York Heart Association class III or IV heart failure</li> </ul>	
	Characteristics		
	Age	Intervention	Control
	Median, years	64.0	65.0
	Range, years	38.0–87.0	31.0–91.0
	Distribution, %		
	18–64 years	53.3	47.5
	$\geq 65$ years	46.7	52.5
	Male sex, %	54.3	58.6
	ECOG performance status, %		
	0–1	89.9	91.2
	2	10.1	8.8

		Cytogenetic risk at study entry, % High risk Standard risk Unknown	12.1 37.1 50.8	13.1 42.9 43.9
<b>Analysis population</b> (continuation)	Characteristics (continuation)	Creatinine clearance Mean, ml/min	85.0±28.9	85.9±30.2
		Distribution, % 30 to < 50 ml/min ≥ 50 ml/min Unknown or other value	6.3 93.4 0.3	7.8 90.4 1.8
		Serum β <sub>2</sub> -microglobulin, % < 2.5 mg/litre ≥ 2.5 mg/litre	19.4 80.6	19.4 80.6
		Previous regimens Median, number Range, number Distribution, % 1 regimen 2 or 3 regimens	2.0 1–3 46.5 53.3	2.0 1–3 39.6 60.1
		Previous therapies, % Bortezomib Lenalidomide	65.9 19.9	65.7 19.7
<b>Descriptive statistics and estimated variability</b>	Treatment group		<i>Intervention</i>	<i>Control</i>
	Number of subjects		396	396
	PFS, months Median 95% CI		26.3 23.3–30.5	17.6 15.0–20.6
	Median OS, months		NE	NE
	24-month OS rates (95% CI), %		73.3 (68.6–77.5)	65.0 (59.9–69.5)
	Number of deaths (%)		143 (36.1)	162 (40.9)
	Best response, number (%)			
	CR or better		126 (31.8)	37 (9.3)
	Stringent CR		56 (14.1)	17 (4.3)
	CR		70 (17.7)	20 (5.1)
	vgPR or better		277 (69.9)	160 (40.4)
	SD or PD		14 (3.5)	59 (14.9)
	ORR, % (95% CI)		87.1 (83.4–90.3)	66.7 (61.8–71.3)
	Clinical benefit rate, % (95% CI)		90.9 (87.6–93.6)	76.3 (71.8–80.4)
	Time to response, months Mean Median		1.6±1.4 1.0	2.3±2.4 1.0
	Duration of response, months Median 95% CI		28.6 24.9–31.3	21.2 16.7–25.8
	QLQ-C30 Global Health Status and Quality of Life scale, least-squares mean estimates <sup>1</sup> Cycle 3, day 1 Cycle 6, day 1 Cycle 12, day 1 Cycle 18, day 1		60.44 62.64 62.32 63.35	57.23 59.30 56.75 58.54

<sup>1</sup> minimal important difference (MID) for between-group differences on the QLQ-C30 Global Health Status/Quality of Life scale is 5 points, 2 and this MID was met at cycle 12 (5.56) and approached at cycle 18 (4.81)

	Median time to progression, months	31.4	19.4
	Median time to next treatment, months	17.3	12.1
<b>Effect estimate per comparison</b>	<i>Comparison groups</i>	<i>Number of subjects (I vs. C)</i>	<i>396 vs. 396</i>
	PFS	HR	0.69
		95% CI	0.57–0.83
		P value	0.0001
	OS	HR	0.79
		95% CI	0.63–0.99
		P value	0.04
	CR or better	HR	NR
		95% CI	NR
		P value	<0.001
	Very good partial response or better	HR	NR
		95% CI	NR
		P value	<0.001
	ORR	HR	NR
		95% CI	NR
		P value	<0.001
	Clinical benefit rate	HR	NR
		95% CI	NR
		P value	<0.001
	Median time to progression	HR	0.62
		95% CI	0.50–0.76
		P value	NR
	<i>PFS subgroup analyses</i>		
	High/standard cytogenetic risk at study entry	Number of subjects (I vs. C)	48/147 vs. 52/170
		HR	0.70/0.66
		95% CI	0.43 – 1.16/0.48 – 0.90
	Previous/No previous treatment with bortezomib	Number of subjects (I vs. C)	261/135 vs. 260/136
		HR	0.70/0.73
		95% CI	0.56-0.88/0.52-1.02
	Previous/No previous treatment with lenalidomide	Number of subjects (I vs. C)	79/317 vs. 78/318
		HR	0.80/0.69
		95% CI	0.52-1.22/0.55-0.85
	Disease responsive/non-responsive to bortezomib in any previous regimen	Number of subjects (I vs. C)	336/60 vs. 335/58
		HR	0.70/0.80
		95% CI	0.57-0.86/0.49-1.30
	Disease nonresponsive/responsive to bortezomib and refractory to immunomodulatory agent in any previous regimen	Number of subjects (I vs. C)	24/27 vs. 372/369
		HR	0.89/0.70
		95% CI	0.45–1.77/0.57–0.85
	Disease refractory/not refractory to immunomodulatory agent in any previous regimen	Number of subjects (I vs. C)	85/311 vs. 88/308
		HR	0.64/0.72
		95% CI	0.44-0.91/0.58-0.90

Abbreviations: CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, NCT = National Clinical Trial, NE = not estimable, NR = not reported, OS = overall survival, PFS = progression-free survival, ORR = overall response rate, PD = progressive disease, PR = partial response, SD = stable disease, vgPR = very good partial response

Table 2: Adverse events (AEs) in the safety population<sup>2</sup>

AE (according to NCI-CTC version 4.0)	Intervention (N=392)		Control (N=389)	
	All grades N (%)	Grade 3 or higher N (%)	All grades N (%)	Grade 3 or higher N (%)
<b>Most common non-haematologic AEs</b>				
Diarrhoea	166 (42.3)	15 (3.8)	131 (33.7)	16 (4.1)
Fatigue	129 (32.9)	30 (7.7)	119 (30.6)	25 (6.4)
Cough	113 (28.8)	1 (0.3)	67 (17.2)	0
Pyrexia	112 (28.6)	7 (1.8)	81 (20.8)	2 (0.5)
Upper respiratory tract infection	112 (28.6)	7 (1.8)	75 (19.3)	4 (1.0)
Hypokalaemia	108 (27.6)	37 (9.4)	52 (13.4)	19 (4.9)
Muscle spasms	104 (26.5)	4 (1.0)	82 (21.1)	3 (0.8)
<b>Other AEs of interest</b>				
Dyspnoea	76 (19.4)	11 (2.8)	58 (14.9)	7 (1.8)
Hypertension	56 (14.3)	17 (4.3)	27 (6.9)	7 (1.8)
Acute renal failure	33 (8.4)	13 (3.3)	28 (7.2)	12 (3.1)
Cardiac failure	25 (6.4)	15 (3.8)	16 (4.1)	7 (1.8)
Ischemic heart disease	23 (5.9)	13 (3.3)	18 (4.6)	8 (2.1)

Abbreviations: AE = adverse event, N = number

The ASPIRE trial [12, 21], a phase III study, evaluated the efficacy and safety of carfilzomib with lenalidomide and weekly dexamethasone (carfilzomib group) compared to lenalidomide and weekly dexamethasone alone (control group) in 792 patients with relapsed multiple myeloma for up to 18 cycles. The starting dose of carfilzomib was 20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1; the target dose was 27 mg/m<sup>2</sup> thereafter. After cycle 18, carfilzomib was discontinued.

Patients with relapsed multiple myeloma and measurable disease who had 1–3 prior treatments were eligible, as well as patients previously treated with bortezomib, provided that they did not have disease progression during treatment. Furthermore, patients who received prior lenalidomide and dexamethasone were eligible if they did not discontinue therapy due to adverse effects, had disease progression during the first 3 months of treatment or had progression at any time during treatment (if lenalidomide plus dexamethasone was their most recent treatment). Patients with grade 3 or 4 peripheral neuropathy (or grade 2 with pain) within 14 days before randomisation, or New York Heart Association were excluded. Median age was 64 years and the majority of the patients (90.5%) had an ECOG performance status of ≤ 1. Of all patients enrolled, less than 13% had a high cytogenetic risk, between 37% and 43% had a standard risk at study entry and in 44% to 51% of patients the cytogenetic risk remained unknown.

**comparing carfilzomib + lenalidomide + dexamethasone with lenalidomide + dexamethasone alone**

**median age of 64 years**

<sup>2</sup> AEs reported in at least 25% of patients in either treatment group and other AEs of particular clinical relevance are listed, including all patients who received at least one dose of the study drug.

<b>previous regimens: bortezomib or lenalidomide</b>	Patients in both groups had received a median of two previous regimens: bortezomib had been administered in 65.9% of patients in the carfilzomib group and in 65.7% of patients in the control group; 19.9% of patients in the carfilzomib group and 19.7% of patients the in control group had received prior lenalidomide therapy.
<b>median PFS significantly improved in carfilzomib group</b>	At interim analysis with a median follow-up of 32.3 months in the carfilzomib group and 31.5 months in the control group respectively, median PFS, the primary endpoint, was 26.3 months (95% CI 23.3–30.5) in the carfilzomib group compared with 17.6 months (95% CI 15.0–20.6) in the control group (HR 0.69 for progression or death, 95% CI 0.57–0.83, $p=0.0001$ ). The PFS benefit was observed across all predefined subgroups. The median OS was not reached in either group, but there was a trend in favour of the carfilzomib group (HR for death 0.79, 95% CI 0.63–0.99). However, since these results are from the interim analysis, they have to be regarded with caution. The 24-month OS rates were 73.3% (95% CI 68.6–77.5) in the carfilzomib group versus 65.0% (95% CI 59.9–69.5) in the control group.
<b>median OS not reached in either group</b>	
<b>ORR was 87.1% (carfilzomib group) vs. 66.7% (control group)</b>	The ORR was 87.1% (95% CI 83.4–90.3) in the carfilzomib group compared to 66.7% (95% CI 61.8–71.3) in the control group ( $p<0.001$ ); complete response or better was achieved by 31.8% (carfilzomib group) and 9.3% (control group) of patients respectively ( $p<0.001$ ). The mean time to a response was 1.6 months in carfilzomib group patients versus 2.3 months in control group patients. The median duration of response was 28.6 months (carfilzomib group) compared to 21.2 months (control group). The clinical benefit rate was 90.9% (95% CI 87.6–93.6) in patients of the carfilzomib group versus 76.3% (95% CI 71.8–80.4) in patients of the control group ( $p<0.001$ ).
<b>median time to progression was prolonged in carfilzomib group</b>	The median time to progression was 31.4 months (carfilzomib group) compared to 19.4 months (control group), resulting in a HR of 0.62 (95% CI 0.50–0.76). The median time to next treatment was 17.3 months in the carfilzomib group and 12.1 months in the control group.
<b>health-related quality of life was improved in the carfilzomib group</b>	365 of 396 patients (carfilzomib group) and 348 of 396 patients (control group) had at least one assessment for health-related quality of life at cycles 1, 3, 6, 12 and 18. Compared to the control group, the patients' health-related quality of life was improved in the carfilzomib group (during 18 cycles of treatment), the $p$ value for overall treatment effect was $p < 0.001$ . The minimal clinically important difference for between-group differences on the QLQ-C30 Global Health Status and Quality of Life scale (5.0 points) was met at cycle 12 and approached at cycle 18.
	In the carfilzomib group, the median duration of treatment was 88.0 weeks (ranging from 1.0 to 185.0 weeks) compared to 57.0 weeks (ranging from 1.0 to 201.0) in the control group.
<b>AEs of grade 3 or higher in 83.7% (carfilzomib group) and 80.7% (control group)</b>	Adverse events (AEs) of grade 3 or higher occurred in 83.7% of carfilzomib-group patients and in 80.7% of control-group patients. Serious AEs were reported by 59.7% (carfilzomib group) and 53.7% (control group) of patients, they occurred most commonly during cycles 1–6 in the carfilzomib group and in cycles > 18 in the control group. AEs of specific interest of grade 3 or higher were dyspnoea (2.8% in the carfilzomib group vs. 1.8% in the control group), cardiac failure (in 3.8% of carfilzomib-group patients and 1.8% of control-group patients), ischaemic heart disease (3.3% of patients in the carfilzomib group and 2.1% of patients in the control group), hypertension (4.3% in the carfilzomib group vs. 1.8% in the control group) and acute renal failure (3.3% in carfilzomib-group patients and 3.1% in control-group patients).



The most common non-haematologic AEs of grade 3 or higher were fatigue (7.7% vs. 6.4% in carfilzomib group and control group respectively) and hypokalaemia, which was reported by 9.4% of carfilzomib-group patients and 4.9% of control-group patients. In terms of haematologic AEs of grade 3 or higher, neutropenia occurred most commonly (29.6% in carfilzomib-group patients and 26.5% in control-group patients); anaemia and thrombocytopenia were reported by 17.9% and 16.6% of patients of the carfilzomib group compared to 17.2% and 12.3% of control-group patients.

In total, 69.9% of patients in the carfilzomib group and 77.9% of control-group patients discontinued treatment, most commonly due to disease progression (39.8% in carfilzomib-group patients and 50.1% in control-group patients) and the occurrence of AEs (15.3% in carfilzomib-group patients and 17.7% in control-group patients). 12.5% of carfilzomib-group patients and 6.9% of control-group patients discontinued treatment due to other reasons (e.g. multiple AEs). Due to AEs, the dose of carfilzomib was reduced in 11.0% of patients; the lenalidomide dose was reduced in 43.3% of carfilzomib-group patients and in 39.1% of control-group patients.

7.7% of patients in the carfilzomib group and 8.5% of control-group patients died during treatment or within 30 days after they received the last dose of the study treatment. Deaths due to AEs occurred in 6.9% of patients in each treatment group. Treatment-related deaths were reported in 14 patients (6 in the carfilzomib group and 8 in the control group); AEs leading to more than 2 deaths in either group were myocardial infarction, cardiac failure and sepsis.

**study treatment discontinuation in 69.9% (carfilzomib group) and 77.9% (control group) of patients**

**treatment-related deaths in 6.9% of patients in each group**

## 6.2 Efficacy and safety – further studies

PX-171-006 was a multicentre, single-arm, open-label phase Ib/II study of carfilzomib, lenalidomide and low-dose dexamethasone in relapsed or progressive multiple myeloma. The aim of the Ib part of the study [22] was to assess safety and to determine the maximum tolerated dose. The phase II part of the dose-expansion study [23] evaluated safety, secondary efficacy endpoints (ORR, PFS, duration of response) and exploratory endpoints (clinical benefit response rate and time to response). In total, 84 patients were included, 52 of whom received the maximum planned dose identified in the phase Ib study. The median age of these 52 patients was 63.0 years and they had received a median of 3 lines of prior therapies. 80.8% had been treated with bortezomib and 73.1% with lenalidomide. Treatment consisted of carfilzomib IV as a 2–10-minute infusion on days 1, 2, 8, 9, 15 and 16 in 28-day cycles, starting with an initial carfilzomib dose of 20 mg/m<sup>2</sup> on days 1 and 2 of the cycle, followed by a dosage of 27 mg/m<sup>2</sup>. Lenalidomide was administered orally at a dose of 25 mg/day on days 1 to 21, and the patients received dexamethasone at 40 mg once weekly. ORR was 76.9%, median PFS was 15.4 months after a median follow-up of 24.4 months and duration of response was 22.1 months. The clinical benefit rate was 76.9 and the patients' median time to response was 0.95 months. Treatment-emergent AEs occurred in all patients, a grade-3 or 4 event in 94.2% and a serious AE in 53.8% of patients respectively. The most common haematologic treatment-emergent AEs of grade 3 or 4 that occurred were lymphopenia (48.1%) and neutropenia (32.7%) followed by anaemia and thrombocytopenia; the most common non-haematologic treatment-emergent

**phase Ib/II study evaluating carfilzomib, lenalidomide and dexamethasone**

	<p>AEs of grade 3 or 4 were hypophosphataemia (25.0%) and fatigue (11.5%). Peripheral neuropathy grade 3 or 4 was observed in 1.9%.</p>
<p><b>FDA approval based on a phase II study (PX-171-003-A1) including 266 patients</b></p>	<p>The FDA's initial (accelerated) approval of single-agent carfilzomib for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent was based on an open-label, single-arm phase II study [24]. A total of 266 patients of this study (PX-171-003-A1) [25] received single-agent carfilzomib at a dose of 20 mg/m<sup>2</sup> IV twice weekly for 3 or 4 weeks in cycle 1, followed by 27 mg/m<sup>2</sup> for ≤ 12 cycles. All patients (median age of 63 years) previously received anti-myeloma therapy; 95% of patients were refractory to their last therapy, 80% were refractory or intolerant to both bortezomib and lenalidomide. The patients received a median of 5 (ranging from 1 to 20) prior lines of therapy, including bortezomib (99.6% of patients), lenalidomide (94% of patients) and thalidomide (75% of patients). Furthermore, patients had previously received corticosteroids, alkylating agents and anthracycline; 74% of patients had a stem cell transplant. ORR (the primary endpoint of the study) was 23.7%; median DOR was 7.8 months. Median OS was 15.6 months, and the median PFS achieved was 3.7 months. The clinical benefit response rate was 37.0%. The most common AEs of grade 3 or 4 were thrombocytopenia (29% of patients), anaemia (24% of patients) and lymphopenia (20% of patients). The most frequent carfilzomib-related AEs of all grades were fatigue (37% of patients), nausea (34% of patients) and thrombocytopenia (29% of patients). The most common AEs associated with treatment discontinuation were hypercalcaemia (associated with progressive disease), congestive heart failure, cardiac arrest, dyspnoea, pneumonia, spinal cord compression and increased serum creatinine. 11 patients (4.1%) died due to an AE.</p>
<p><b>assessing single-agent carfilzomib in pretreated patients</b></p>	<p>Safety data for the FDA approval of carfilzomib were evaluated in 526 patients with relapsed multiple myeloma who received carfilzomib as monotherapy [15].</p>
<p><b>impact of cytogenetic abnormalities evaluated in patients of PX-171-003-A1 trial</b></p>	<p>Jakubowiak et al. [26] prospectively evaluated the impact of cytogenetic abnormalities on outcomes during the PX-171-003-A1 trial. In this multicenter, open-label, single-arm, phase 2 study, single-agent carfilzomib was administered intravenously over 2–10 minutes on days 1, 2, 8, 9, 15 and 16 of each 28-day cycle. The cytogenetic status was available in 229 patients; 72.9% had standard-risk cytogenetics and 27.1% were high-risk patients. The ORR was 25.8% in the high-risk subgroup and 24.6% in the standard-risk subgroup; the clinical benefit rate was 30.7% in the high-risk group and 40.7% standard-risk subgroup. The incidence of progressive disease was 22.6% in the high-risk subgroup compared to 27.5% in the standard-risk subgroup. Due to progressive disease within the first 2 cycles, 29.0% (high-risk subgroup) and 20.4% (standard-risk subgroup) of patients discontinued study treatment. Median OS was 9.3 months (high-risk subgroup) versus 19.0 months (standard-risk subgroup); median PFS was 3.5 months in the high-risk subgroup versus 4.6 months in the standard-risk subgroup.</p>
<p><b>pilot phase II study of single-agent carfilzomib in 46 patients</b></p>	<p>PX-171-003-A0, an open-label, single-arm, multicentre, pilot phase II study [27] evaluated single-agent carfilzomib in 46 patients with relapsed and refractory multiple myeloma after ≥ 2 prior therapies including bortezomib and an immunomodulator. Carfilzomib was administered IV at a dosage of 20 mg/m<sup>2</sup> on days 1, 2, 8, 9, 15 and 16 every 28 days for up to 12 cycles; additionally, dexamethasone (4 mg orally or IV) pre-medication was given. Due to results of the PX-171-002 study [28] that became available while this study was ongoing, the carfilzomib dose was escalated to 27 mg/m<sup>2</sup> in 3 patients</p>

(starting at cycles 8, 9 and 10, respectively). The ORR, the primary endpoint, was 16.7%, the clinical benefit response rate was 23.8%. The median duration of response achieved was 7.2 months (for the ORR population) and 13.8 months (for patients achieving minimal response or better); the estimated median time to progression was 3.5 months and median PFS was 3.5 months; 76.2% of patients had progressive disease or died. The most common haematologic AEs of grade 3 or 4 were anaemia (37.0% of patients), lymphopenia (28.3% of patients) and thrombocytopenia (26.1% of patients). Other frequent AEs of grade 3 or 4 occurring were hyponatraemia (13.0% of patients) and renal/acute renal failure in 13.0% of patients. Peripheral neuropathy was seen in 15.2% of patients with all but one case being grade 1 or 2.

Lendvai et al. [29] conducted a single-arm, single-centre, open-label phase II study in 44 patients with relapsed multiple myeloma. They received carfilzomib as a 30-minute IV infusion on days 1, 2, 8, 9, 15 and 16 of a 28-day cycle. On days 1 and 2 of cycle 1, carfilzomib was administered at a dose of 20 mg/m<sup>2</sup>, followed by a dose escalation to 56 mg/m<sup>2</sup> if tolerated. Low-dose dexamethasone (20 mg/m<sup>2</sup>) could have been added to restore anti-myeloma activity and to prolong treatment in patients whose disease progressed after achieving at least a partial response after 2 cycles and in patients who had not achieved at least a partial response after 2 cycles. The study population (median age of 63 years) was heavily pretreated with a median of 5 (ranging from 1 to 11) prior lines of therapy; all patients had received prior bortezomib and an immunomodulatory agent (thalidomide/lenalidomide). 72% of the patients had had prior autologous stem cell transplantation and 22% had prior allogeneic stem cell transplantation. 77% of patients were refractory to bortezomib and 64% of patients were refractory to both bortezomib and lenalidomide. ORR was 55% of which 31% of patients achieved at least a partial response. The median PFS was 4.1 months, the median OS was 20.3 months (after a median follow-up of 18.4 months). The most frequent treatment-emergent non-haematologic AEs of any grade occurring in ≥ 20% of patients were diarrhoea, nausea, fatigue, headache and constipation. The most common carfilzomib-related, treatment-emergent non-haematologic AEs of any grade occurring in ≥ 20% of patients were fatigue, nausea, headache and upper respiratory infection. The most frequent treatment-emergent AEs of grade 3 or 4 occurring in ≥ 5% of patients were lymphopenia (50%), leukopenia (43%), thrombocytopenia (39%) and anaemia (36%); the most common non-haematologic treatment-emergent AEs of grade 3 or 4 were hypertension (25%), heart failure (20%), and pneumonia (18%).

An open-label, single-arm phase II study [30] evaluated single-agent carfilzomib in patients with relapsed and/or refractory multiple myeloma. A total of 35 patients (median age of 63 years), all previously treated with bortezomib, were enrolled. The median number of prior therapies was 3.0; 97.1% received prior corticosteroid therapy, other commonly used drugs were alkylating agents (88.6% of patients), thalidomide (68.8% of patients) and lenalidomide (37.1% of patients). 77.1% of patients received prior therapy with thalidomide or lenalidomide. 20% of patients were refractory to bortezomib, 62.9% were refractory to their last therapy regardless of the administered drug. The patients received carfilzomib IV at a dose of 20 mg/m<sup>2</sup> over 2 to 10 minutes on days 1, 2, 8, 9, 15 and 16 of every 28-day cycle for up to 12 cycles; prophylactic dexamethasone (4 mg/day) was given prior to each dose of carfilzomib during the first cycle. 17.1% of patients achieved an ORR of 31.4% and a clinical benefit response rate. The median duration of response was > 10.6 months, the median time to progression was 4.6 months. The most

**phase II study of carfilzomib with/without low-dose dexamethasone**

**phase II trial of single-agent carfilzomib in patients pretreated with bortezomib**

common non-haematological AEs of all grades were fatigue (62%), nausea (60%) and vomiting (42.9%); the most common haematological AEs of all grades were anaemia (34.3%), thrombocytopenia (31.4%) and neutropenia (25.7%). Most frequently occurring haematological AEs of grade 3 or higher were thrombocytopenia (20%), anaemia (14.3%) and neutropenia (11.4%). The most common non-haematological AEs of grade 3 or higher were pneumonia (8.6%), dyspnoea, upper respiratory infection, hypertension, hypercalcaemia and epiglottitis (each 5.7%).

**phase II study of  
carfilzomib in patients  
with renal impairment**

Pharmacokinetics and safety of carfilzomib in multiple myeloma patients with renal impairment was assessed in an open-label, multicentre phase II study [31]. A total of 50 patients (median age of 64 years) with varying degrees of renal impairment and a median of 5 prior therapies (including corticosteroids, bortezomib, lenalidomide, thalidomide, alkylating agents, SCT and anthracyclines) were included. 66% of patients were refractory to prior bortezomib therapy. 46% of patients were refractory to both bortezomib and lenalidomide. According to creatinine clearance, they were assigned to 5 groups: > 80 ml/min, 50–80 ml/min, 30–49 ml/min, < 30 ml/min and chronic haemodialysis. The patients received a median number of 5 prior therapies and a median of 4 cycles of carfilzomib. Carfilzomib was administered at a dose of 15 mg/m<sup>2</sup> in cycle 1; if tolerated, the dose was increased to 20 mg/m<sup>2</sup> at cycle 2 and to 27 mg/m<sup>2</sup> at cycle 3 and in subsequent cycles. Dexamethasone was administered prophylactically (4 mg); additionally, to improve response, patients with less than partial response after cycle 2 or less than complete response after cycle 4 were eligible to receive dexamethasone at a dose of 20 mg prior to each dose of carfilzomib. Analyses showed no differences in carfilzomib clearance or exposure in patients, neither in patients with normal renal function nor in patients with renal impairment. The most common AEs of all grades (occurring in ≥25% of patients) were fatigue (56%) anaemia (50%), diarrhoea and nausea (each 36%). The most frequent haematologic AEs of grade 3 or 4 occurring in ≥ 5% of patients were anaemia (28%), thrombocytopenia (20%) and lymphopenia (18%). Fatigue (14%), pneumonia (12%) and pain (10%) were the most common non-haematologic AEs of grade 3 or 4 occurring in ≥ 5% of patients.

**combination of  
panobinostat and  
carfilzomib**

Berdeja et al. [32] assessed the combination of panobinostat and carfilzomib in patients with relapsed/refractory multiple myeloma in 44 patients who had relapsed after at least one prior treatment. The study was conducted as a phase I/II, single-arm, open-label multicentre trial. The patients had a median age of 66 years and received a median of 5 prior therapies including bortezomib (89%), immune-modulating drugs (89%) and SCT (52%). 36% of patients were refractory to proteasome inhibitors, 30% were refractory to immune-modulating drugs, 14% were refractory to both bortezomib and immune-modulating drugs and 43% were refractory to their last treatment. The patients received panobinostat on days 1, 3, 5, 15, 17 and 19, the established expansion dose was 30 mg. Carfilzomib was given on days 1, 2, 8, 9, 15 and 16 of each 28-day cycle, the expansion dose was established at 20/45 mg/m<sup>2</sup>. Treatment was continued until progression or intolerable toxicity. The results showed an ORR of 67% for all patients; 67% for patients refractory to prior proteasome inhibitor treatment and 75% for patients refractory to prior immune-modulating drug treatment. Median PFS was 7.7 months; median time to progression was also 7.7 months. Median OS had not been reached at a median follow-up of 17 months. The most common treatment-related toxicities of grade 3 or 4 were thrombocytopenia (38% of patients), neutro-

penia (21% of patients) and fatigue (11% of patients). One treatment-related death (2%) was reported.

## 7 Estimated costs

There is currently no cost information available regarding carfilzomib (Kyprolis®) for Austria.

According to data from Germany, one vial of carfilzomib at 60 mg (obtained via International Pharmacy) costs € 1,432.76 [13] which is the same like in the US [1]. Assuming an average body surface of 1.8 m<sup>2</sup> and a dosage of 20 mg/m<sup>2</sup> on days 1 and 2 and a dosage of 27 mg/m<sup>2</sup> on days 8, 9, 15 and 16, patients receive a total dose of 266 mg of carfilzomib in the first cycle. In cycles 2 to 12, a total dose of 292 mg of carfilzomib (6 infusions at 27 mg/m<sup>2</sup>) is administered per cycle. Thus, for cycles 1 to 12, 5 vials of carfilzomib are needed per cycle if any left-overs can be re-used, resulting in costs of € 7,163.8 per cycle or in € 8,596.6 if new vials have to be used for each administration. In cycles 13 to 18, 4 doses of carfilzomib (at 27 mg/m<sup>2</sup> on days 1, 2, 15 and 16) are given in each cycle, resulting in costs of € 5,731.04 per cycle. In total, for 18 cycles of carfilzomib treatment, costs of € 120,351.84 would incur. Additionally, costs for lenalidomide, dexamethasone, and antiviral and anti-thrombotic prophylaxis incur. This cost estimation is based on the dosage scheme of the ASPIRE trial [21].

**no cost information  
available for Austria**

**costs for 1 cycle:  
€ 5,731– € 7,164  
(depending on the  
number of infusions  
per cycle)**

## 8 Ongoing research

In June 2015, a search in two databases ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)) was conducted and the following trials were identified:

**3 ongoing phase III  
trials identified**

- ✱ NCT01568866 (EudraCT number 2012-000128-16): ENDEAVOR is a phase III, randomised open-label trial, comparing carfilzomib plus dexamethasone with bortezomib plus dexamethasone in patients with relapsed multiple myeloma. The estimated study completion date is March 2019; the estimated primary completion date is January 2016.
- ✱ NCT01302392 (EudraCT number 2009-016840-38): This open-label, randomised phase III trial (FOCUS) evaluates the efficacy of carfilzomib versus best supportive care in patients with relapsed and refractory multiple myeloma who have received all available approved treatment options and would otherwise be offered palliative care. The estimated study completion date is December 2015.
- ✱ NCT02412878: ARROW, an open-label, randomised phase III study in patients with relapsed and refractory multiple myeloma receiving carfilzomib plus dexamethasone compares one-weekly versus twice-weekly carfilzomib dosing. Estimated study completion date is September 2018.

**numerous  
phase II trials**

Numerous phase II studies evaluate the use of carfilzomib in multiple myeloma in different dosages (e.g. weekly carfilzomib dose of 70 mg/m<sup>2</sup> in patients who are refractory to 27 mg/m<sup>2</sup>) or in various combination regimens, including combinations with bendamustine, panobinostat, vorinostat, pegylated liposomal doxorubicin, pomalidomide, ibrutinib or selinexor. Furthermore, studies assess carfilzomib in different patient populations, such as younger transplantation-eligible patients or elderly, symptomatic patients. There is also a large number of ongoing phase II trials, assessing carfilzomib in other malignancies, e.g. mantle-cell lymphoma, neuroendocrine cancer, renal cell cancer, prostate cancer).

## 9 Commentary

**approved by the FDA,  
but not by the EMA**

In the US, carfilzomib (Kyprolis®) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy and as a single agent for the treatment of patients with multiple myeloma who have received at least two prior therapies [8]. In Europe, the EMA granted orphan designation for carfilzomib for the treatment of multiple myeloma in 2008 [9] but marketing authorisation is still outstanding.

The FDA's initial (accelerated) approval was based [15] on the results of a single-arm, open-label phase II study [25], evaluating the efficacy and safety of single-agent carfilzomib in 266 patients. Additionally, safety data were evaluated in 526 patients with relapsed multiple myeloma who had received carfilzomib as monotherapy. Moreover, and as a condition for accelerated approval in 2012, the manufacturer had to submit the complete analysis of the ASPIRE trial [15].

**PFS significantly  
improved in  
carfilzomib group**

**ORR and health-  
related quality of life  
were improved in  
carfilzomib group**

This phase III trial was conducted in 792 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy [21]. Interim analyses showed a median PFS of 26.2 months for patients receiving carfilzomib in combination with lenalidomide and dexamethasone, resulting in a gain of 8.7 months compared to patients treated with lenalidomide and dexamethasone only; risk reduction for PFS was 31%. The ORR was improved in the carfilzomib group (87.1%) compared to the control group (66.7%). Patients of the carfilzomib group achieved higher rates for complete response or better (31.8% vs. 9.3%) and for very good partial response or better (69.9% vs. 40.4%). Median OS was not yet reached in either group at the time of interim analysis; the Kaplan-Meier 24-month OS rates were 73.3% in the carfilzomib group versus 65.0% in the control group. In the carfilzomib group, health-related quality of life measured with the QLQ-C30 Global Health Status and Quality of Life scale showed a clinically important difference at 12 weeks in comparison to the control group.

**serious AEs in 59.7%  
(carfilzomib group)  
and 53.7% (control  
group) of patients**

AEs of grade 3 or higher were reported from 83.7% of carfilzomib-group patients and 80.7% of control-group patients; serious AEs were reported from 59.7% (carfilzomib group) and 53.7% (control group) of patients; they occurred most commonly during cycles 1 to 6 in the carfilzomib group and in cycles > 18 in the control group. 7.7% of patients of the carfilzomib group



and 8.5% of the control group died during treatment or within 30 days after they received the last dose of study treatment [21].

Safety data were also evaluated in a study summarising the results of 526 patients participating in 4 phase II trials of single-agent carfilzomib [33]. In terms of AEs of specific interest for multiple myeloma, including neuropathy, cardiac and renal AEs, the authors reported the following: peripheral neuropathy occurred in 7% of patients. A cardiac disorder AE of any kind occurred in 22.1% of patients. In terms of renal AEs, 33.1% of patients had at least one grouped renal impairment AE including increased blood creatinine, acute renal failure, increased blood urea and decreased renal creatinine clearance [33].

Although the results of the ASPIRE trial concerning PFS, ORR and to some extent patients' quality of life show improvements for these outcomes, further data are needed to better characterise the role of carfilzomib in the treatment of multiple myeloma, since several questions remain unanswered:

- ❖ **Carfilzomib versus bortezomib:** The superior results of the ASPIRE study were obtained by add-on of carfilzomib to lenalidomide and dexamethasone in comparison to lenalidomide and dexamethasone. However, the comparison to bortezomib, also a proteasome inhibitor, is of high interest. Bortezomib is a reversible inhibitor, whereas carfilzomib is a covalent inhibitor. In vitro, carfilzomib showed greater selectivity and less off-target activity than bortezomib and was active in cell lines that are resistant to bortezomib [34]. Moreover, the occurrence of peripheral neuropathy, an adverse effect limiting the use of bortezomib, seems to be reduced with carfilzomib administration [35, 36]. However, treatment costs for bortezomib are lower.

The results of the ENDEAVOR study (NCT01568866; currently only published only as abstract [37]) comparing carfilzomib with dexamethasone to bortezomib with dexamethasone might help to clarify this question; however, the maximum dose of carfilzomib was escalated to 56 mg/m<sup>2</sup> in this trial and is therefore considerable higher than that used in the ASPIRE study.

- ❖ **Role of carfilzomib:** Generally, the role of carfilzomib in multiple myeloma treatment, considering line of treatment and combination with other agents needs to be determined. On the one hand, it is currently in phase III for the treatment of newly diagnosed multiple myeloma. On the other hand and as mentioned above, some bortezomib-resistant cell-lines respond to carfilzomib treatment [4, 34]. Even though carfilzomib was licensed for heavily pretreated patients based on phase II study results in the US [25], comparative data for patients non-responding/refractory to other available treatment options is scarce. In the ASPIRE trial, only 6% of patients were non-responsive/refractory to bortezomib and an immunomodulatory agent and 15% did not respond to bortezomib. Further data from the FOCUS trial (scheduled until December 2015) comparing single agent carfilzomib with best supportive care in patients who have received all available approved treatment options will help to clarify that question.

Also, since carfilzomib is currently being studied as single agent but also in combination with other agents such as ibrutinib, bendamustine or panobinostat, a pan-deacetylase inhibitor, the best combination regimen, needs to be determined.

## open questions

### carfilzomib vs. bortezomib

### role of carfilzomib

**efficacy in high risk patients?**

✧ **Influence of cytogenetic status:** Since the cytogenetic status of patients is evaluated after multiple myeloma has been diagnosed [3], the impact of cytogenetic abnormalities needs to be assessed. Even though subgroup analyses of the ASPIRE trial indicated that no difference exists between patients with high risk and standard risk cytogenetic profile and phase II study results support this finding [26, 29], only 53% of patients had been tested for cytogenetic mutations. Overall, 100 patients (13%) had a high cytogenetic risk at study entry and cytogenetic risk was unknown in 47% of patients in the ASPIRE study [21].

**novel agents can be administered orally**

✧ **Role of novel agents for anti-myeloma therapy:** The role of other proteasome inhibitors and monoclonal antibodies in development for the treatment of multiple myeloma needs to be determined. Novel proteasome inhibitors including ixazomib (MLN9708, a boronic acid) with reversible inhibiting mechanism, oprozomib (ONX-0912, an exo-pyketone) and marizomib (NPI0052, a salinosporide), which are irreversible inhibitors, are currently under investigation [38].

Since some of these new agents can be administered orally, the role of carfilzomib in comparison to these emerging proteasome inhibitors remains to be seen; although patients may strongly prefer oral options, their comparative efficacy and side-effect profiles are still under investigation [34]. The taxing administration scheme of carfilzomib requiring patients to receive intravenous infusions on six days per month might limit the application of carfilzomib, especially when effective oral drugs are available.

In terms of anti-CD38 monoclonal antibodies, particularly elotuzumab (anti-CS1) in combination with lenalidomide and dexamethasone has shown promising results [38]. Recently published results of a phase II study of single-agent daratumumab showed durable activity, deep responses and a favourable safety profile in patients with  $\geq 3$  lines of prior therapy and or double-refractory multiple myeloma [39].

**optimal dosage and schedule**

✧ **Optimal dosage and schedule:** The currently approved dosing for carfilzomib is 20 mg/m<sup>2</sup> initially, with a dose escalation, if tolerated to 27 mg/m<sup>2</sup> [11]. However, higher doses (up to 56 mg/m<sup>2</sup>) of carfilzomib were tolerable in phase I/II settings and are used in phase III trials [29]. Whether higher doses yield improved outcomes with manageable side-effects is still unknown. In any case, treatment costs would increase further.

**applicability of study results**

✧ **Applicability of study results:** The ASPIRE trial study population had a median age of 64 years and more than 50% of them had already received 2 or 3 previous treatment regimens [21]. Regarding that the median age at diagnosis of multiple myeloma is 69 years [6], the study population of the ASPIRE trial was considerably younger. Moreover, the majority (90.5%) of the study population had a good performance status of 0–1. These facts need to be considered concerning the applicability of the study results. With regard to heavily pre-treated patients, the results of the FOCUS trial (NCT01302392), conducted in patients who had received at least 3 prior therapies, will be of interest.

Patients with relapsed/refractory multiple myeloma are a heterogeneous population and several treatment options exist [40]. No standard treatment of patients with relapsed and/or refractory multiple myeloma exists and the appropriate treatment depends on the disease status, the patient status or the drug components administered in initial therapy. For patients with multiple



myeloma, the optimal combination regimens and timing of administration need to be determined; furthermore, patients need to be treated in future clinical trials [40]. Generally, combination regimens are preferred over monotherapy, and three-drug combination regimens are administered frequently. Although they might demonstrate superior efficacy regarding response rates, their effect on PFS and OS is not as clear [41].

Despite the promising results of the ASPIRE trial, further evidence is needed to prove the efficacy (especially regarding overall survival) and safety of carfilzomib and to determine its role for the treatment of multiple myeloma. The most efficacious and safe combination with other drugs and the optimal line of treatment for carfilzomib administration needs to be assessed. Moreover, the patient population most suitable for carfilzomib treatment needs to be evaluated. Many issues have to be resolved, not least in light of the high cost of carfilzomib therapy.

**further evidence  
is needed**

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